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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/571,069	12/07/2006	Hidemi Kurihara	0230-0245PUS1	2459

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EXAMINER	
BORGEEST, CHRISTINA M	
ART UNIT	PAPER NUMBER
1649	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/571,069	KURIHARA ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 18-30* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 18-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-16 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 17 April 2009 has been entered.

Formal Matters

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649, Examiner Christina Borgeest.

Response to Amendment

Claims 1-30 are pending in the instant application. Claims 10 and 30 are amended, claim 17 is cancelled and Claims 1-9 and 18-29 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Claims 10-17 and 30 are under examination in the instant office action.

Rejections Withdrawn

Claim Rejections - 35 USC § 112, second paragraph

The rejection of claims 10-17 and 30 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in response to Applicants' amendments and to their cancellation of claim 17.

The rejection of claim 10 for being vague and indefinite in its recitation of periodontal transplant comprising an effective "tissue regenerating amount" of a neurotrophic factor and "a periodontically acceptable scaffold material" is withdrawn in response to Applicants' amendment.

The rejection of claims 11-16 because the terms "regenerates", "prevents" and "enhances" are relative terms which renders the claim indefinite is withdrawn upon reconsideration and in response to Applicants' explanation at p. 8, last 3 paragraphs.

The rejection of claims 11-16 and 30 for insufficient antecedent basis for the limitation "therapeutically effective amount" in claim 10 is withdrawn in response to Applicants' amendment of claim 10 to recite "therapeutically effective amount".

The rejection of claim 30 as being vague and indefinite in its recitation of an effective amount per "defect of furcation" is withdrawn upon further consideration and

Applicants' submission of evidence indicating that furcation is a term of art meaning an extension of periodontal pockets that occur between the roots of multi-rooted teeth.

Claim Rejections - 35 USC § 102

The rejection of claims 10-16 under 35 U.S.C. 102(b) as being anticipated by Kirker-Head, Advanced Drug Delivery Reviews, 43:65-92, 2000 as set forth at paragraphs 13-16 of the Office action mailed 17 November 2008 is withdrawn in response to Applicants' amendment and upon reconsideration. Specifically, the amendment of claim 10 to recite that the neurotrophic factor is selected from the group consisting of a brain-derived neurotrophic factor (BDNF), a nerve growth factor (NGF), neurotrophin-3 (NT-3) or neurotrophin-4/5 (NT-4/5) limits the claims to those growth factors and the Kirker-Head reference teaches BMP-2. Furthermore, claim 13 requires that the periodontal transplant regenerates the alveolar bone, but the Kirker-Head reference teaches at p. 77, left column, 2nd paragraph that an BMP-2/absorbable collagen sponge matrix composite was evaluated for alveolar ridge augmentation and the results showed no significant bone growth. Finally, with regard to claim 14, there is no evidence in Kirker-Head that any periodontal transplant containing BMPs could prevent the apical invasion of gingival epithelium along the dental root surface.

Claim Rejections - 35 USC § 103

The rejection of claim 17 and 30 under 35 U.S.C. 103(a) as being unpatentable over as applied to claims 10-16 above, and further in view of Tsuboi et al., J Dent Res,

80(3): 881-886 (2001); Kurihara et al., J Periodontol, 74(1):76-84, January 2003; and Harada et al., Arch Hisol Cytol, 66(2): 183-194, May 2003 as set forth at paragraphs 17-20 of the Office action mailed 17 November 2008 is withdrawn in response to Applicants' cancellation of claim 17 and the amendment of claim 10, which now recites the neurotrophic factor is selected from the group consisting of a brain-derived neurotrophic factor (BDNF), a nerve growth factor (NGF), neurotrophin-3 (NT-3) or neurotrophin-4/5 (NT-4/5), thus overcoming the rejection under 35 U.S.C. 102(b), upon which this rejection was built.

New Rejections

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-16 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 recites "wherein the neurotrophic factor is selected from the group consisting of a brain-derived neurotrophic factor, a nerve growth factor, neurotrophin-3 or neurotrophin-4/5." It is not clear whether Applicants mean to specifically claim "brain-derived neurotrophic factor" and "nerve growth factor" or, whether by the recitation of the article "a" before brain-derived neurotrophic factor and nerve growth factor, they mean to claim a broader class of neurotrophic factors. The claims must particularly

point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant (see MPEP 2171). Claims 11-16 and 30 do not remedy this defect, thus are also rejected for depending upon an indefinite claim. Note that this rejection could be overcome by amending the claims to delete the article “a” before brain-derived neurotrophic factor and nerve growth factor.

Claims 10 and 30 recite “a periodontal transplant which comprises a therapeutically effective amount of a neurotophic factor”, but fail to state what the therapeutically effective amount is effective to do. In other words, the claims are indefinite because the claims do not clearly define what the therapeutically effective amount achieves and therefore the body of the claim does not relate back to the preamble. See MPEP 2173.05 for guidance ("The phrase “an effective amount” has been held to be indefinite when the claim fails to state the function which is to be achieved and more than one effect can be implied from the specification or the relevant art. In re Fredericksen 213 F.2d 547, 102 USPQ 35 (CCPA 1954)). For the purpose of prior art, the claims are interpreted as a periodontal transplant comprising any amount of a neurotrophic factor. Note that this rejection can be overcome by amending the claims to reciting what the therapeutically effective amount achieves, for instance, as in claims 11-16.

Claim 30 recites the limitation "wherein the therapeutically effective amount is in the range of 1×10^{-12} to 1×10^{-3} g per tooth or defect of furcation" in claim 10. There is

insufficient antecedent basis for this limitation in the claim because claim 10 does not recite “per tooth or defect of furcation.” Since claim 10 does not recite “per tooth or defect of furcation,” this further renders indefinite what component of the transplant must be “in the range of 1 X 10^{-12} to 1 X 10^{-3} g."

Claim Rejections - 35 USC § 112, first paragraph – Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988) These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure with the enablement

requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 14 recites "[t]he periodontal transplant according to claim 10, wherein the therapeutically effective amount prevents the apical invasion of gingival epithelium along the dental root surface." The issue is that total prevention of this process of apical invasion of gingival epithelium along the dental root surface is not possible, as it is a process that all experience in a varying degree with advancing age. The plain English meaning of the word prevention implies 100% success at stopping an event from occurring. A therapeutic device such as the periodontal transplant claimed can inhibit or ameliorate symptoms and/or onset of disease, but it cannot completely prevent the apical invasion of gingival epithelium along the dental root surface, as this is a natural process of aging. The aging process can be slowed in some cases, but not prevented. There are no working examples indicating that the apical invasion of gingival epithelium along the dental root surface is completely preventable using the claimed device. While the literature suggests strategies for delaying the onset of this process, it is silent with respect to complete prevention of this aging related process.

Due to the large quantity of experimentation necessary to manufacture a periodontal device capable of the prevention of the apical invasion of gingival epithelium along the dental root surface, the lack of direction/guidance presented in the specification regarding and the absence of working examples directed to the same, the complex nature of the invention (i.e., prevention of an aging-related process) and the

state of the art, which does not teach that aging related processes are preventable, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10-13, 15, 16 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirker-Head and further in view of Wikesjö 2003 (J Periodontal. May 2003; 74: 635-647—hereafter "Wikesjö 2003), Tsuboi et al. (J Dent Res, 2001; 80(3): 881-886—of record), Kurihara et al. (J Periodontol, 2003 74: 76-84—of record) and Harada et al., (Arch Histol Cytol. 2003; 66: 183-194—of record). The amended claims are drawn to a periodontal transplant comprising an absorbent material and a neurotophic factor selected from the group consisting of a brain-derived neurotrophic factor (BDNF), a nerve growth factor (NGF), neurotrophin-3 (NT-3) or neurotrophin-4/5 (NT-4/5), wherein said transplant regenerates the periodontal ligament, the alveolar bone, the dental pulp, repairs dentin in the pulp cavity and wherein the therapeutically effective amount of BDNF, NGF, NT-3 or NT-4/5 is in the range of 1×10^{-12} to 1×10^{-3} g per tooth or defect of furcation. As stated above in the Rejections under 35 U.S.C. 112, second paragraph, claim 30 lacks antecedent basis, thus it is unclear what component of the transplant is required to be within the recited range, thus in rejection, the claim limitation of 1×10^{-12} to 1×10^{-3} g is not afforded patentable weight.

The first factor to consider when making a rejection under 35 U.S.C. 103(a) is to determine the scope and contents of the prior art. Kirker-Head teaches at p. 77, left column, 2nd paragraph, that BMPs are useful for treatment of periodontal disease including regeneration of periodontal ligament, bone, cementum and gingiva. Kirker-

Head teaches at p. 77, left column, 3rd paragraph the ability of a BMP-2/absorbable collagen sponge composite able to increase maxillary sinus floor thickness, enhanced osseointegration; p. 77, right column, 1st paragraph, BMPs repaired dentine formation and maintained pulp vitality. In other words, Kirker-Head suggests to one of skill in the art that a periodontal transplant containing a growth factor and an absorbent material is capable of regenerating the periodontal ligament, bone, cementum and repair dentine formation and maintain pulp vitality. This would be instructive to one of skill in the art, who, upon reading this reference would understand that a periodontal transplant containing a growth factor and an absorbent material shows strong promise for treating periodontal disease.

The second factor to consider when making a rejection under 35 U.S.C. 103(a) is to ascertain the differences between the prior art and the claims at issue. As stated above, the Kirker-Head reference suggests that BMP-2 does not regenerate alveolar bone when combined with an absorbable collagen matrix. However, Wikesjö 2003 teaches how to make a periodontal transplant for regenerating bone and soft tissue using an absorbent material, namely a bioresorbable, space-providing polyglycolic acid-trimethylene carbonate membrane (PGA-TMC) that was combined with BMP-2 (see p. 637, left column, 2nd paragraph through right column, 1st paragraph). Wikesjö 2003 report that sites receiving the PGA-TMC/BMP-2 combination exhibited substantial alveolar bone and cementum regeneration (see p. 639, right column; p. 641, left column, 1st paragraph; p. 642, right column; p. 643, left column). In addition, Wikesjö 2003 teach that the PGA-TMC membrane provides for alveolar bone and cementum

regeneration and guided tissue regeneration (a functionally oriented periodontal ligament—see p. 645, left column, last paragraph). Wikesjö 2003 conclude that the PGA-TMC membrane is suitable for guided tissue regeneration, soft tissue healing and bone regeneration. Finally, Wikesjö 2003 identify the importance of the material used for the periodontal implant in their discussion in the right column of p. 636, namely, macroporous devices are beneficial for guided tissue regeneration and that

> "limitations of BMP-2 technologies have been reported relative to the biomaterials evaluated as carriers. In particular, carrier limitations have restricted the biologic potential of BMP-2 for indications where soft tissue compressive forces may limit the space for bone formation. The objective of this study was to evaluate a space providing macroporuous, bioabsorbable polyglycolic acid-trimethylene carbonate membrane inteeded for GTR and to evaluate this bioabsorbable device in presence of rhBMP-2..." (See last full paragraph at p. 636—citations omitted by Examiner).

In other words, Wikesjö 2003 presented a solution to a problem known in the art by Kirker-Head. Wikesjö 2003 discuss at length the background of different materials used for periodontal implants in the introduction at p. 636. The Wikesjö 2003 reference clearly articulates the problem at p. 636, right column, where it states it is "critical that biomaterials developed for clincal use receive considerable scrutiny" and "limitations of rhBMP-2 technologies have been reported relative to biomaterials evaluated as carriers...In particular, carrier limitations have restricted the biologic potential of rhBMP-2 for indications where soft tissue compressive forces may limit the space for bone formation." This guides one of ordinary skill in the art towards the construction of a periodontal implant that allows for maximum bone growth and soft tissue regeneration when combined with use of a growth factor.

The other difference between the prior art and the claims at issue was addressed by the previous Examiner, who pointed out explicitly at p. 7 2nd paragraph of the previous Office action that the Kirker-Head reference does not teach the transplant comprising BDNF. With regard to this difference, the teachings of Tsuboi et al., Kurihara et al., and Harada et al., demonstrate that BDNF was known in the art as a specific trophic factor for periodontal cells and tissues. In addition to teaching expression of neurotrophins in mouse periodontal ligament (MPL) cells, Tsuboi teach that BDNF induced proliferation of MPLs (Tsuboi Figure 3). Tsuboi et al. also demonstrate that periodontal ligament cells (i.e., soft tissue) contain BDNF. Tsuboi conclude that "the expression of neurotrophins and TRK receptors in periodontal ligament cells, which are among the targets of trigeminal neurons, suggests the maintenance or recovery of function in the periodontal ligament cells and neurons in tissue regeneration." (See p. 885, left column, last paragraph). Kurihara indicate that BDNF regenerates periodontal tissue (see abstract; p. 82, right column, last paragraph) and that BDNF upregulated DNA synthesis in human periodontal ligament cells (p. 81, right column, last full paragraph). Kurihara suggests that the neurotrophins "secreted from cells in periodontal tissue [i.e., BDNF] may play important roles in survival and differentiation of neurons during inflammation and wound healing in periodontal tissue and in the innervation of periodontal tissue after regenerative treatment and tooth replant or transplant treatment." (See p. 81, left column, penultimate paragraph). Harada teaches that BDNF regenerates periodontal nerves (see whole document, for example, p. 192, penultimate paragraph). The combined teachings of Tsuboi, Kurihara

and Harada, contrary to Applicants' assertions, suggest strongly that neurotrophins and their receptors are expressed during tooth development and regeneration, and that they play a role in periodontal disease and periodontal tissue regeneration. Finally, it is noted that Tsuboi et al. demonstrate that BDNF in the range of 1×10^{-12} to 1×10^{-3} g enhanced periodontal cell proliferation (see Figure 3-C at p. 884). Upon reading the combined teachings of Tsuboi et al., Kurihara et al., and Harada et al., one of ordinary skill in the art would come to the conclusion that BDNF is an important factor in periodontal tissue regeneration.

The combined teachings of the cited references segues into the third factor to be considered when making a rejection under 35 U.S.C. 103(a), which is to resolve the level of ordinary skill in the pertinent art. The skill in the art is dental arts is high, and the Kirker-Head reference indicates that it was well known that a periodontal transplant containing a growth factor and an absorbent material shows strong promise for treating periodontal disease. Furthermore, Wikesjö 2003 presented a solution to a known problem in the art, namely, that the material of the periodontal transplant is vital in the promotion of healing. The teachings of Tsuboi et al., Kurihara et al., and Harada et al., demonstrate that BDNF was known in the art to as a specific trophic factor for periodontal cells and tissues. Given that there is a limited number of trophic factors that could be used to treat periodontal disease, it would be obvious to one of ordinary skill in the art to try and make a periodontal transplant, as shown in Kirker-Head and Wikesjö 2003 containing BDNF because the combined references of Tsuboi et al., Kurihara et al., and Harada et al. indicate that BDNF is important in periodontal tissue regeneration.

As stated above, there are a finite number of predictable compositions available for use with the periodontal transplant. For instance, this is evidenced by Tsuboi et al., who demonstrate that periodontal ligament cells (i.e., soft tissue) contain BDNF, thus this would suggest to one of skill in the art that BDNF is among one of the limited neurotrophic factors available to try when constructing a periodontal transplant. In short, periodontal transplants containing growth factors were known in the art, and this was evidenced by the Kirker-Head and Wikesjö references. The combined teachings of Tsuboi et al., Kurihara et al., and Harada et al. suggest to one of ordinary skill in the art that BDNF is one among a finite list of factors that would likely have success in treatment of periodontal disease.

This segues into a discussion of the fourth "Graham factor", which is to consider objective evidence present in the application indicating obviousness or nonobviousness. As Applicants indicate, the specification shows in vitro data that alveolar bone, cementum and periodontal ligament are regenerated by BDNF. The experimental findings of Applicants are not unobvious over those disclosed in the Kirker-Head and Wikesjö 2003 references. The Kirker-Head reference teaches periodontal transplants comprising a periodontically acceptable scaffold (collagen sponge) material and neurotrophic factor. The collagen sponge as taught by this reference is equivalent within the art to the Teruplug® embodiment in the working examples of the specification at p. 43 of the specification. The Kirker-Head reference teaches sponges imbued with BMPs enhance osseointegration and strengthen bone as well as regenerate periodontal tissues. The Wikesjö 2003 reference provides guidance to one of ordinary skill in the

art regarding maximizing the effect of growth factors through choosing the right material for the periodontal transplant device. Thus, there are no surprising results with respect to the periodontal transplant device. There are also no surprising results with respect to the fact that BDNF is a neurotrophic factor important in periodontal disease. For instance, with regard to BDNF, Kurihara et al., like the instant specification, report that neurotrophins are expressed in periodontal ligament cells. Given that BDNF is one among a finite list of factors that would likely have success in treatment of periodontal disease, the person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp, i.e., it would be obvious to try to make a periodontal transplant containing a neurotrophic factor selected from the group consisting of BDNF. If this leads to the anticipated success, it is likely to be the product not of innovation but of ordinary skill and common sense.

Response to Arguments

Although Applicants' arguments are made over the now withdrawn rejection (set forth at paragraphs 17-20 of the Office action mailed 17 November 2008) over claims 17 and 30 under 35 U.S.C. 103(a) as being unpatentable over Kirker-Head (of record), as applied to claims 10-16, and further in view of Tsuboi et al. (of record); Kurihara et al. (of record) and Harada et al. (of record), the arguments are applicable to the current rejection of claims 10-13, 15, 16 and 30 under 35 U.S.C. 103(a) as being unpatentable over Kirker-Head and further in view of Wikesjö 2003,, Tsuboi et al., Kurihara et al. and Harada et al., thus the arguments will be addressed below.

Applicants argue at p. 12, 2nd paragraph that since the Examiner did not resolve the Graham factors, the rationale the Examiner provides for combining the cited references is improper.

It is the opinion of this Examiner that the previous Examiner addressed the Graham factors implicitly, however, in deference to Applicants, the current Examiner addressed the factors explicitly in turn in the current rejection under 35 U.S.C. 103(a) above. In addition, the current Examiner will address the factors in the response to Arguments.

Applicants argue at p. 12, 3rd – 4th paragraphs through p. 13, whole page that it is not obvious for the skilled artisan to combine the Kirker-Head reference with the above cited references indicating effects of BDNF on periodontal tissue because periodontal tissues are composed of both hard and soft tissues and that Tsuboi discloses only expression of neurotrophins in mouse periodontal ligament (MPL) cell line, Kurihara indicates only potential contribution of neurotrophins to regeneration of periodontal tissue (i.e., hard tissue) from in vitro data and Harada suggests involvement of BDNF in the regeneration of periodontal nerves.

The first factor to consider when making a rejection under 35 U.S.C. 103(a) is to determine the scope and contents of the prior art. As stated above, Kirker-Head teaches at p. 77, left column, 2nd paragraph, that BMPs are useful for treatment of periodontal disease including regeneration of periodontal ligament, bone, cementum and gingiva. Kirker-Head teaches at p. 77, left column, 3rd paragraph the ability of a BMP-2/absorbable collagen sponge composite able to increase maxillary sinus floor thickness, enhanced osseointegration; p. 77, right column, 1st paragraph, BMPs repaired dentine formation and maintained pulp vitality. In other words, Kirker-Head suggests to one of skill in the art that a periodontal transplant containing a growth factor and an absorbent material is capable of regenerating the periodontal ligament, bone, cementum and repair dentine formation and maintain pulp vitality. This would be

instructive to one of skill in the art, who, upon reading this reference would understand that a periodontal transplant containing a growth factor and an absorbent material shows strong promise for treating periodontal disease. The second factor to consider when making a rejection under 35 U.S.C. 103(a) is to ascertain the differences between the prior art and the claims at issue. The previous Examiner pointed out explicitly at p. 7 2nd paragraph that the Kirker-Head reference does not teach the transplant comprising BDNF. The teachings of Tsuboi et al., Kurihara et al., and Harada et al., demonstrate that BDNF was known in the art as a specific trophic factor for periodontal cells and tissues. In addition to teaching expression of neurotrophins in MPL cells, Tsuboi teach that BDNF induced proliferation of periodontal cells (Tsuboi Figure 3). Tsuboi et al. also demonstrate that periodontal ligament cells (i.e., soft tissue) contain BDNF. Tsuboi conclude that "the expression of neurotrophins and TRK receptors in periodontal ligament cells, which are among the targets of trigeminal neurons, suggests the maintenance or recovery of function in the periodontal ligament cells and neurons in tissue regeneration." (See p. 885, left column, last paragraph). Kurihara indicate that BDNF regenerates periodontal tissue (see abstract; p. 82, right column, last paragraph) and that BDNF upregulated DNA synthesis in human periodontal ligament cells (p. 81, right column, last full paragraph). Kurihara suggests that the neurotrophins "secreted from cells in periodontal tissue [i.e., BDNF] may play important roles in survival and differentiation of neurons during inflammation and wound healing in periodontal tissue and in the innervation of periodontal tissue after regenerative treatment and tooth replant or transplant treatment." (See p. 81, right column, penultimate paragraph).

Harada teaches that BDNF regenerates periodontal nerves (see whole document, for example, p. 192, penultimate paragraph). The combined teachings of Tsuboi, Kurihara and Harada, contrary to Applicants' assertions, suggest strongly that neurotrophins and their receptors are expressed during tooth development and regeneration, and that they play a role in periodontal disease and periodontal tissue regeneration. Finally, it is noted that Tsuboi et al. demonstrate that BDNF in the range of 1×10^{-12} to 1×10^{-3} g enhanced periodontal cell proliferation. Upon reading the combined teachings of Tsuboi et al., Kurihara et al., and Harada et al., one of ordinary skill in the art would come to the conclusion that BDNF is an important factor in periodontal tissue regeneration.

The combined teachings of the cited references segues into the third factor to be considered when making a rejection under 35 U.S.C. 103(a), which is to resolve the level of ordinary skill in the pertinent art. The skill in the art is dental arts is high, and the Kirker-Head reference indicates that it was well known that a periodontal transplant containing a growth factor and an absorbent material shows strong promise for treating periodontal disease. The teachings of the of Tsuboi et al., Kurihara et al., and Harada et al., demonstrate that BDNF was known in the art to as a specific trophic factor for periodontal cells and tissues, and given that there is a limited number of trophic factors that could be used to treat periodontal disease, it would be obvious to one of ordinary skill in the art to try and make a periodontal transplant, as shown in Kirker-Head, containing BDNF because the combined references of Tsuboi et al., Kurihara et al., and Harada et al. indicate that BDNF is important in the periodontal tissue. As stated above, there are a finite number of predictable compositions available for use with the

periodontal transplant. For instance, this is evidenced by Tsuboi et al., who demonstrate that periodontal ligament cells (i.e., soft tissue) contain BDNF, thus this would suggest to one of skill in the art that BDNF is among one of the limited neurotrophic factors available to try when constructing a periodontal transplant. In short, periodontal transplants containing neurotrophic and growth factors were known in the art, and this was evidenced by the Kirker-Head reference. The combined teachings of Tsuboi et al., Kurihara et al., and Harada et al. suggest to one of ordinary skill in the art that BDNF is one among a finite list of factors that would likely have success in treatment of periodontal disease. The person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely to be the product not of innovation but of ordinary skill and common sense.

Applicants argue at p. 13, last full paragraph that Wikesjö et al. (submitted by Applicants—of record) teach that BMP-2 was capable of regenerating alveolar bone but was not effective in regenerating cementum or periodontal ligament and that ankylosis was observed.

This argument is not found persuasive, because there is evidence in the art that the findings of Wikesjö et al. was a result of the material they used for the periodontal transplant. See a later publication by Wikesjö et al. (J Periodontal. May 2003; 74: 635-647—"Wikesjö 2003"). Wikesjö 2003 teach that BMP-2 enhances bone regeneration and soft tissue healing when combined with a bioabsorbable space-providing macroporous membrane containing polyclycolic acid-trimethylene carbonate (see abstract; whole article). Wikesjö 2003 addresses the earlier article in their discussion at the right column of p. 642, where they point out that cementum regeneration was

significant when a macroporous membrane was used with or without the BMP-2 and that the earlier study described use of an absorbable collagen sponge in conjunction with BMP-2 "without provisions for GTR [guided tissue regeneration]." Wikesjö 2003 identify the importance of the material used for the periodontal implant in their discussion in the right column of p. 636, namely, macroporous devices are beneficial for GTR and that

> "limitations of rhBMP-2 technologies have been reported relative to the biomaterials evaluated as carriers. In particular, carrier limitations have restricted the biologic potential of rhBMP-2 for indications where soft tissue compressive forces may limit the space for bone formation. The objective of this study was to evaluate a space providing macroporuous, bioabsorbable polyglycolic acid-trimethylene carbonate membrane intended for GTR and to evaluate this bioabsorbable device in presence of rhBMP-2..." (See last full paragraph at p. 636—citations omitted by Examiner).

Given the teachings of Wikesjö 2003, it seems likely that the report of the previous Wikesjö publication, namely that BMP-2 was capable of regenerating alveolar bone but was not effective in regenerating cementum or periodontal ligament, was likely a result of the material used in the construction of the periodontal transplant.

Applicants conclude arguments at p. 14 that the present inventors have shown based upon in vitro data that alveolar bone, cementum and periodontal ligament are regenerated by BDNF.

This segues into a discussion of the fourth "Graham factor", which is to consider objective evidence present in the application indicating obviousness or nonobviousness. As Applicants indicate, the specification shows in vitro data that alveolar bone, cementum and periodontal ligament are regenerated by BDNF. The experimental findings of Applicants are not unobvious over those disclosed in the Kirker-Head

reference. The Kirker-Head reference teaches that periodontal transplants comprising a periodontically acceptable scaffold (collagen sponge) material and neurotrophic factor. The collagen sponge as taught by the reference is equivalent within the art to the Teruplug® embodiment in the working examples of the specification at p. 43. The Kirker-Head reference teaches sponges imbued with BMPs enhance osseointegration and strengthen bone as well as regenerate periodontal tissues. There are no surprising results with respect to either the periodontal transplant device or the fact that BDNF is a neurotrophic factor important in periodontal disease. The findings reported in the specification that neurotrophins are expressed in periodontal ligament cells are not unobvious over findings in Kurihara et al. Given that BDNF is one among a finite list of factors that would likely have success in treatment of periodontal disease, the person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp, i.e., it would be obvious to try to make a periodontal transplant containing a neurotrophic factor selected from the group consisting of BDNF. If this leads to the anticipated success, it is likely to be the product not of innovation but of ordinary skill and common sense.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is (571)272-4482. The examiner can normally be reached on 9:00am - 3:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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